DOCKET NO: 216261US0CONT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

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| IN RE APPLICATION OF | : |
| DARIO CREMASCHI, ET AL. | : EXAMINER: NICKOL, G.B. |
| SERIAL NO: 09/988,150 | : |
| FILED: NOVEMBER 19, 2001 | : GROUP ART UNIT: 1642 |
| FOR: USE OF MICROPARTICLES HAVING A PROTEIN AND AN ANTIBODY ADSORBED THEREON FOR PREPARING A PHARMACEUTICAL COMPOSITION FOR INTRANASAL ADMINISTRATION | : |

# REPLY BRIEF

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

This is in reply to the Examiner's answer mailed January 11, 2006.

The claimed invention would not have been obvious in view of the combination of Smith et al (WO94/28879), Bomberger (U.S. patent no. 5,879,712), and Almeida et al (J. Drug Targeting, 1996, vol. 3, pages 455-467) for the simple facts that

(1) the prior art would not have been combined in the manner alleged by the office to yield a method for intranasal administration of a composition of a microparticle having a protein and an antibody specific for the protein absorbed thereon, by contacting this complex with the nasal mucosa of a patient; and

(2) evidence, in the form of experimental data, has been provided which demonstrates an unexpectedly improved outcome when the claimed method is performed compared to that of the prior art of Smith et al.

Concerning point (2), this evidence constitutes secondary considerations rebutting any case of obviousness, assuming one actually existed. In fact, the Office has already recognized that the claimed method which yields the results of these unexpectedly improved transepithelial transport through the nasal mucosa is patentable over the very same three references. (See "Status of Claims," page 2 of the Examiner's answer dated January 11, 2006, indicating that claim 20, among others, are allowable of this cited art). Of particular noteworthiness, is the fact that both claim 11 (subject to the rejection) and claim 20 (allowable) both include a limitation of administering the same microparticle complex to the nasal mucosa. So, what's the difference? The difference is that claim 20 includes the values obtained from the data set when the method of claim 11 has been performed. Clearly then, the rejection of claim 11 is unsustainable since the Office has already recognized the merits of the data as evidence of non-obviousness when viewed in light of the cited art. The rejection should be reversed.

The Examiner at page 4, 4th paragraph of the Examiner's Answer acknowledges that the primary reference (Smith et al.) "does not teach 'intranasal' administration." For this deficit, the Office relies on Bomberger et al and Almeida et al to "provide the requisite motivation to include intranasal administration." (page 5, 1st paragraph of the Examiner's answer). In relying on Almeida et al and rebutting Appellants points of distinctions, the Examiner at page 7, 2nd paragraph of the Examiner's Answer states "Almeida expressly teaches the superior advantages associated with intranasal administration (Almeida, page 457, col. 1)." However, as stated in Appellants Brief in the paragraph bridging in the paragraph bridging pages 4-5, the Examiner has focused on one particular section of Almeida as opposed to the reference in its entirety as required (MPEP § 2142.02 citing to *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)). As discussed in Appellant's Brief at the top of page 5,

Almeida, when discussing particle mediated delivery of drugs actually suggests that absorption through the intestinal and nasal mucosa are similar. In other words,, while Almeida, generally lists advantages of nasal delivery of drugs in general, when Almeida is read in its entirety, Almeida would suggest similar mechanisms of absorption and not the vastly improved levels as described in the present specification (to be discussed further below).

In fact, it would appear that the Examiner has agreed that intestinal and nasal mucosa absorption would be similar: "the epithelial lining the intestine and the epithelial cells lining the nasal mucosa may participate in solid particle uptake in the same fashion" (page 8, 1st paragraph, last sentence of the Examiner's answer). Further reading of this sentence of the Examiner's answer is as follows: "there is no evidence to suggest that this mechanism negatively effects the volume or flow of material transported across the epithelium." Once again, the Examiner mischaracterizes Appellant's arguments. Appellants did not argue that Almeida suggests a negative flow, only that the intestinal absorption and nasal absorption are similar—as opposed to the 'superior advantages' espoused by the Examiner in providing some reason to combine Smith with Almeida.

At page 8, 2nd paragraph through page 9, 1st paragraph of the Answer, the Examiner discounts Bomberger's explicit disclosure of "releasing the drug contained therewithin" and suggests that the disclosure in col. 3, starting at line 27 compensates for this disclosure of an encapsulated drug. However, col. 3 is the 'Background' section of Bomberger and relates to problems with prior methods that Bomberger is attempting to solve. The disclosure as to the impractability of the encapsulated ICAM molecule is only specific to the methods to which Bomberger is discussing in the background and not as it relates to the Bomberger invention.

On page 9, 1st paragraph of the Answer, the Examiner states that "it would appear that Appellant has argued and discussed the references individually without clearly addressing the

combined teachings." This is incorrect. First, it is noted to argue why the combination of references fails to render a claimed invention obvious, one must first undertake an analysis of each of the relevant teachings of the cited art as it may, or may not, contribute to the motivation to combine and whether the prior art suggests all claim limitations. Second, Appellants were not arguing the references individually but rather explaining why the Smith particles would not necessarily be administered intranasally based on Almeida and Bomberger: (1) If one reads Almeida's entire disclosure, Almeida teaches that for the purposes of microcapsule delivery of drugs, the absorptions in intestines and nasal mucosa are similar and thus does not support the Examiner's contention that Almeida suggests to use the Smith particles intranasally; and (2) Bomberger's encapsulated microparticles are different and not generally applicable to any situation as in the Smith delivery vehicles . Therefore, as the alleged motivation for intranasal delivery is based on the disclosures of Almeida and Bomberger and this motivation is not found in the references themselves but rather a hindsight reconstruction of the claims, the claimed method would not have been obvious in view of the combined art cited in support of the Examiner's rejection.

On page 10, lines 7-9 of the Answer, the Examiner discounts the data presented in the specification stating "it remains unclear why appellant believes the comparison between the *in vivo* conditions versus the *in vitro* conditions is experimentally "appropriate"." First, this entire line of reasoning, i.e., discounting the data as evidence of nonobviousness, has been improperly raised for the first time in the Examiner's answer—noting that such Examiner arguments had never been made of record in this case before, having had ample opportunity to do so, i.e. the data were provided in the originally filed specification. In fact, the only real criticism of the data was presented in the Office Action of April 9, 2004 on pages 4-5: "this argument has been considered but is only found persuasive to the extent that the greater than expected rate of transepithelial transport is recited in the claims." Thus, it is submitted that

the Examiner's entire line of reasoning and opinion relating to the data as set forth in the Answer be given no weight in deciding the issues in this case.

In response to the Examiner's meritless conclusion concerning the data, Appellants have made it abundantly clear, on the record, why the *in vitro* and *in vivo* test data are comparable. For the sake of brevity, rather than reproducing the entire explanation here, reference is provided to the paragraph bridging pages 7-8 of Appellant's Brief.

On page 10, 1st paragraph, last sentence of the Answer, the Examiner once again criticizes the data, stating: "it appears that it would be unscientific to perform these experiments using nasal epithelium @ 37°C." As discussed on page 7, 1st paragraph of Appellants Brief, citing to page 9 of the specification, the nasal mucosa experiments were performed at 27°C not 37°C. Therefore, this basis for discounting the merit of the data as evidence of nonobviousness has no merit whatsoever.

Finally, the Examiner has alleged that the data presented in the specification be afforded little, if any weight, because "Appellant's specification does not compare these results to any historical perspective." (page 11, lines 15-16 of the Answer). Once again, this is the first time that such a criticism has been raised by the Examiner, having had ample opportunities to do so before, and should be given no consideration at this late stage. Nonetheless, in response, Appellants note that the relevant comparison in terms of the prior art (historically, using the Examiner's words), is the closest prior art not some unknown or hypothetical historical indicia now alleged by the Examiner. The closest prior art, as admitted by the Examiner is Smith (it is the primary reference relied upon in the rejection at issue). Appellants have compared intestinal delivery (as taught by Smith) to intranasal delivery (as claimed) and have shown a marked improvement which the Inventors have deemed surprising (see page 4, lines 4-8 of the present specification).

The Examiner's position is not based in the facts or the law. The Inventors statements remain uncontested by any technical information and merely an unsubstantiated opinion of the Examiner. Therefore, the data provided in the specification supports Appellant's position that these data are evidence of nonobviousness. Nothing the Examiner has stated nor cited to suitably contradicts this evidence.

In sum, the prior art cited by the Examiner in the rejection under 35 USC 103 does not support a *prima facie* case of obviousness and clear, unambiguous data have been provided which shows a surprising improvement of delivery when compared to the closest prior art. In view of this evidence, the rejection under 35 USC 103 must be reversed.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.
Norman F. Oblon

Customer Number
22850

Daniel J. Pereira, Ph.D.
Registration No. 45,518